03-C-0058: Phase I Trial of Pirfenidone in Children with Neurofibromatosis Type 1 and Plexiform Neurofibromas

Neurofibromatosis Type 1 (NF1) is an autosomal dominant, progressive genetic disorder characterized by diverse clinical manifestations. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system including plexiform neurofibromas (PNs), which may cause severe morbidity and possible mortality. The histopathology of these tumors suggests that events connected with formation of fibroblasts might constitute a point of molecular vulnerability. Gene profile analysis demonstrates overexpression of fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor in PNs in patients with NF1. Pirfenidone is a novel anti-fibrotic agent that inhibits these and other growth factors. Clinical experience in adults has demonstrated that pirfenidone is effective in a variety of fibrosing conditions and pirfenidone is presently under study in a phase II trial for adults with progressive PNs. There are no data concerning the toxicity or efficacy of pirfenidone in children. A phase I trial of pirfenidone will be performed in children with NF1 and plexiform neurofibromas to determine the maximum tolerated dose or "comparable dose", toxicities, and pharmacokinetics of pirfenidone. Pirfenidone will be administered orally three times a day (q8h) for cycles of 28 days with no rest period.

ELIGIBILITY CRITERIA:

Age: ≥3 years and ≤21 years of age. Required body surface area (BSA) for first dose level (750 mg/m^2/day) 0.61 m^2, for second dose level (1500 mg/m2/day) 0.31 m^2.

Diagnosis: Patients with NF1 and plexiform neurofibromas that have the potential to cause significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or significant cosmetic problems, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a plexiform neurofibroma is clinically suspected. In addition to plexiform neurofibroma(s), all study subjects must have at least one other diagnostic criteria for NF1 listed below (NIH Consensus Conference):

- Six or more café-au-lait spots (≥0.5 cm in prepubertal subjects or ≥1.5 cm in postpubertal subjects)
- Freckling in the axilla or groin
- Optic glioma
- Two or more Lisch nodules
- A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)
- A first-degree relative with NF1

In this study a plexiform neurofibroma is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal plexiform neurofibroma involves two or more levels with connection between the levels or extending laterally along the nerve.

Measurable Disease: Patients must have measurable plexiform neurofibroma(s). For the purpose of this study a measurable lesion will be defined as a lesion of at least 3 cm measured in one dimension.

Prior Therapy: Patients must not have plexiform neurofibromas that can be easily surgically removed. A surgical consultation is recommended prior to enrollment on the study to evaluate if tumor resection is a feasible option.

Since there is no standard effective chemotherapy for patients with NF1 and plexiform neurofibromas, patients may be treated on this trial without having received prior medical therapy.

- Patients must have recovered from the toxic effects of all prior therapy before entering this study. The Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) Version 2.0 will be used for toxicity assessment. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). Recovery is defined as a toxicity grade <2.
- Patients must have had their last dose of radiation therapy to the site of the plexiform neurofibroma at least 90 days prior to study entry, and their last dose of chemotherapy, immunotherapy, or hormonal therapy directed to the tumor, at least 30 days prior to study entry.

Performance Status: Patients > 10 years must have a Karnofsky performance level ≥ 50, and children ≤ 10 years must have a Lansky performance level ≥ 50. (See Appendix 2). Patients who are wheelchair bound because of paralysis should be considered "ambulatory" when they are up in their wheel chair.

Hematologic Function: Patients must have an absolute granulocyte count ≥1,500/μL , a hemoglobin ≥ 9.0 gm/dl, and a platelet count ≥150,000/μL at study entry.

Hepatic Function: Patients must have a bilirubin within normal limits and SGPT ≤ 2x upper limit of normal.

Renal Function: Patients must have an age-adjusted normal serum creatinine (see table below) OR a creatinine clearance ≥ (70 mL/min/1.73 m^2).

Age (Years)	**Maximum Serum Creatinine** (mg/dl)
< 5	0.8
5 ≤ age <10	1.0
10 ≤ age <15	1.2
≥15	1.5

Informed Consent: All patients or their legal guardians (if the patients is <18 years old) must sign an IRB approved document of informed consent (screening protocol) prior to performing studies to determine patient eligibility. After confirmation of patient eligibility all patients or their legal guardians must sign the protocol specific informed consent to document their understanding of the investigational nature and the risks of this study before any protocol related studies are performed (other than the studies which were performed to determine patient eligibility). When appropriate pediatric patients will be included in all discussion. Age appropriate assent forms for children from 7 through 12 years, and for children from 13 through 17 years have been developed and will be signed by the pediatric patients in order to obtain written assent.

- Patients must be able to take pirfenidone by mouth. Capsules can be opened and content mixed with food for easier consumption in small children.
- Patients (both male and female) must be willing to practice birth control (including abstinence) during and for two months after treatment, if of a child-bearing age. For purposes of the protocol, all patients greater than 9 years of age or those showing pubertal development will be considered of childbearing age.

EXCLUSION CRITERIA

- Pregnant or breast feeding females are excluded, because the toxic effects and pharmacology of pirfenidone in the fetus and newborn are unknown.

- Clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate pirfenidone or are likely to interfere with the study procedures or results.
- Evidence of an active optic glioma requiring treatment with chemotherapy or radiation therapy or malignant glioma or a history of malignant peripheral nerve sheath tumor or other cancer.
- An investigational agent within the past 30 days.
- Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, or immunotherapy.
- Inability to return for follow-up visits or obtain follow-up studies required to assess toxicity and response to therapy.
- Prior treatment with pirfenidone.

PRETREATMENT EVALUATION

- History and physical, inculding documentaion of meanusreable disease, performance status, signs and symptoms, height, weight, BSA
- Laboratory work including CBC/differential, Chemistries, urine or serum pregnancy within 2 weeks prior to enrollment
- Quality of Life assessment: IPI questionaire for patient and parent for patients ≥6 < 18 years of age.
- Radiographic Evaluation: MRI scan of all known plexiform neurofibromas including the progressing PN within 2 weeks of enrollment on study.
- Tissue procurement: biopsy of plexiform, only if clinically indicated.

GENERAL TREATMENT PLAN:

- This is a phase I, open label, dose escalation trial of oral pirfenidone in pediatric patients with NF1 and inoperable, sympotomatic plexiform neurofibromas that have the potential to cause significant morbidity. Pirfenidone will be administered orally as capsules three times a day (approximately q8hours) for cycles of 28 days with no rest period between cycles (28 day treatment cycle). The starting dose of pirfenidone is 750 mg/m^2/day, rounded to the nearest 100 mg. Intrapatient dose escalations will occur in patients treated on dose levels 1 and 2 after completion of the first treatment cycle provided pirfenidone is tolerated on the prior cycle.

PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES:

- Blood samples for determination of pirfenidone plasma concentrations will be obtained after the first dose on cycle 1 only. The second and third doses of pirfenidone will not be administered during the pharmacokinetic sampling on day 1.

HOSPITALIZATION: Not anticipated

ACCRUAL: The trial is open to accrual. Patients meeting eligibility criteria can be referred to the Pediatric Oncology Branch, NCI, for evaluation. Patients should bring to NIH a summary of previous treatment, most recent laboratory work, copies of recent radiologic studies, and original pathology slides and report if available.